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General anesthetics interaction with pentameric ligand-gated ion channel GLIC: Insights from ONIOM calculations

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Background: Around the turn of the last century, Meyer and Overton demonstrated the correlation of olive oil solubility with anesthetic potency over a range of agents. Their original theory of anesthetic action proposed that since the largest source of cellular lipid components belonged to the cell membrane, anesthetics must, therefore, act by dissolving in and perturbing the nature of nerve cell membranes so as to produce the state of general anesthesia. However, since that time much protein mutational data as well as gross exceptions to this correlation have been found which not only imply a necessary hydrophilic component to anesthetic action, but also further demonstrate an ion channel protein mechanism of action, the nature of which is yet to be elucidated at an atomic level. While our previous work on the anesthetic-protein interactions has demonstrated the polarization of otherwise hydrophobic agents within a bound protein environment, it was limited by the rudimentary computational software and hardware of the time, as well as the limited availability of anesthetic-protein crystal coordinates. The work presented here now demonstrates, in a more rigorous manner, how quantum mechanics combined with molecular mechanics can reveal the true nature of interactions between the general anesthetics and the Pentameric Ligand-Gated Ion Channels (pLGICs) across several complexes of the bacterial homologue from *Gloeobacter violaceus* (GLIC) with different anesthetics.

Methods: All calculations were performed using the Discovery Studio 4.1 software suite and the ONIOM method implemented in the Gaussview 5.0 and Gaussian 09 programs. The coordinate files (PDB) for the complexes of pentameric ligand-gated ion channel GLIC (pH-gated bacterial homologue from *Gloeobacter violaceus*) with anesthetics desflurane (3P4W), propofol (3P50), bromoform (4HFH) and ketamine (4F8H) were obtained from the RCSB. These PDB files were prepared by adding hydrogens, setting AMBER force-field parameters and optimizing the hydrogen geometries. An inner protein cavity within 10 angstroms of the anesthetic was carved out for each complex within which three ONIOM layers were defined as follows: a high layer involving the anesthetic ligand alone where density functional method could be applied using the hybrid meta exchange-correlation functional M06-2X with the 6-31+G* basis set; a middle layer involving residues within 4 angstroms of the ligand where PM6 semi-empirical quantum mechanics could be employed; and a lower level layer from 4 angstroms to 10 angstroms where the AMBER molecular mechanics force-field could be implemented. The hydrogens and the anesthetic ligand then underwent geometry optimization while the protein backbone remained fixed. The Root-Mean-Square Deviation (RMSD) between the optimized structure and the crystal structure is applied as a criterion to evaluate any distortion of the ligand binding modes. Analyses of interaction energies, binding features, charge distributions and electrostatic potential surfaces were then performed for bound and unbound states of the ligand.

Results: As in our previous work, three-layer ONIOM calculations continued to reveal that except for the anesthetic propofol within GLIC, other anesthetics' binding sites within the GLIC are amphiphilic, not just hydrophobic. Anesthetic-GLIC interactions include several van der Waals interactions and other weak polar interactions. However, our current work allows the elucidation of additional results. Geometry optimization of the ligand within the binding site produced minimal alteration in position of the ligand to that of the original crystal structure, but did reveal presence of hydrogen bonding and halogen bonding between anesthetic and protein moieties. The steric effects within the binding sites play a dominant role in the anesthetic-GLIC interactions over the polarization effects, and the steric effects cause a significant asymmetry in the otherwise symmetric atomic charge distributions of the symmetric ligands in vacuo.

Conclusions: The rigorous three-layer ONIOM calculations combined higher level quantum mechanics with lower level quantum mechanics and molecular mechanics, which not only reveal the amphiphilic nature of anesthetic-GLIC interactions except for the propofol, but also show the domination of steric effect within the binding site as well as the existence of hydrogen bonding and halogen bonding potential.

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